

A Complete Profile on Blind-your-eye Mangrove *Excoecaria agallocha* L. (*Euphorbiaceae*): Ethnobotany, Phytochemistry, and Pharmacological Aspects

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ABSTRACT

Traditional system of medicine consists of large number of plants with various medicinal and pharmacological importances. This article provides a comprehensive review of the complete profile of an important mangrove plant *Excoecaria agallocha* L. (*Euphorbiaceae*) and elaborately describing the ethnobotany, phytochemistry, and pharmacological properties. It is used traditionally in the treatment of various diseases such as epilepsy, ulcers, leprosy, rheumatism, and paralysis. The latex obtained from the bark is poisonous in nature and may cause temporary blindness, thus it is also known as the blind-your-eye mangrove plant. Many phytoconstituents were isolated from the plant, which were mainly diterpenoids, triterpenoids, flavonoids, sterols, and few other compounds. The plant also showed many pharmacological activities such as antioxidant, antimicrobial, anti-inflammatory, analgesic, antiulcer, anticancer, antireverse transcriptase, antihistamine-release, antifilarial, DNA damage protective, antidiabetic, and antitumor protecting activities. Hence, this review could help guide researchers anticipating to undertake further investigations in these directions.

Key words: Diterpenoids, *Euphorbiaceae*, *Excoecaria agallocha*, mangrove, pharmacology, phytoconstituents

INTRODUCTION

Medicinal plants are considered an important component of flora and are distributed widely throughout India.^[1] From the dawn of civilization, medicinal plants are considered part and parcel of human society to combat diseases.^[2] Majority of the world's population rely wholly or partially on traditional system of medicine for their principle health care needs. A survey conducted by the World Health Organization (1993), the traditional medicinal practitioners deals with about 80% patients in India, 90% patients in Bangladesh, and 85% patients in Burma.^[3] In the recent past years, there has been an increase in the use of health products derived from plants in developed as well as developing countries which resulted in an exponential growth of herbal products globally. An upward trend has been observed in the research on herbs.^[4] In the present scenario, most of the drugs are obtained from plants sources such as morphine from the dried latex of unripe seedpods of *Papaver somniferum* poppy, atropine is obtained from *Atropa belladonna*, ephedrine obtained from *Ephedra vulgaris*, and reserpine from *Rauwolfia serpentina*. The secondary metabolites found in the medicinal plants are regarded as the potential source of drugs and thus are of immense therapeutic value. Medicines derived from medicinal plants are also easily available, safer, economical, and effective.^[3]

Mangroves have long been a source of astonishment to the layman and of interest for the scientists. The word "mangrove" may be derived by conjunction of the English word "grove" with Portuguese word "mangue," the Spanish word "mangle," "manglier" which is a French word or the Malay word "manggi-manggi." A book named "The Mangroves and Us" by Marta Vannucci (1989) explains that the word is neither Portuguese nor Spanish, but the word 'mangue' derives from the national language of Senegal. It is possible that the Portuguese first adapted the word, later to be modified by the Spanish, as a result of their exploration of the coast of west Africa.^[5]

Mangroves are woody halophytic plants which are ecologically of great importance. They act as a source of energy in coastal food chain and also protects against various natural calamities such as cyclone and tsunami. Many drugs, dyes, and tannins are obtained from the mangroves. Mangroves usually constitute from about eighty families of shrubs and trees which inhabits the shoreline and estuaries in the tropical and subtropical coastal regions of the world. They also function as natural nutrient filters and recyclers, protect coastal areas from seawater intrusion, and also helps in floodwater mitigation.^[6]

The genus *Excoecaria* comprises nearly forty species which are distributed in the mangrove region of Asia, Africa, and northwest Australia.^[7] The milky latex discharged from *Excoecaria agallocha* bark is poisonous and may cause temporary blindness and blistering of the skin.^[8] The latex is also well known for its biocidal effects on marine organisms and phytoplankton, causes metabolic depression of the rice

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field crab, *Oziotelphusa senex* and is used as an uterotonic, fish poison, dart poison, and contains novel chalcones and piperidine alkaloids.^[9] *E. agallocha* usually shed their leaves annually. Unlike most mangrove species, they do not have specialized aerial roots called pneumatophores that extend above the soil surface and supply the underground roots with oxygen.^[10]

This review article gives a critical description about the complete profile of the mangrove plant *E. agallocha* L., and mainly highlighting the various ethnobotanical uses, phytochemical constituents isolated, and pharmacological studies conducted on this plant.

Taxonomical Classification

the details of the taxonomic position of *Excoecaria agallocha* L. is given in [Table 1].^[11]

Vernacular Names of *Excoecaria agallocha* L.

Excoecaria agallocha L. is also known by several vernacular names as it is distributed in the mangrove region of various parts of India. The details of the vernacular names are mentioned in [Table 2].^[12]

Geographical Distribution

E. agallocha L. is widely distributed in mangrove forests throughout Asia, Australia, and Southern pacific region of the world. Details are given in [Table 3].^[13]

Botanical Description

E. agallocha L. is a mangrove plant belonging to family *Euphorbiaceae*. It is a small tree which usually grows up to 15 m in height [Figure 1]. The full description of its botanical features has been tabulated in [Table 4].^[14,15]

Ethnobotanical Information

The plant is known to play an important economical, ecological as well as medicinal role.^[16] It is traditionally used in the treatment of ulcers, sores, and stings from poisonous marine creatures, and also functions as an emetic and purgative. Treatment of rheumatism, leprosy, and paralysis is also cured by the bark oil obtained from *E. agallocha*.^[17] It is also used traditionally in the treatment of conjunctivitis, dermatitis, and hematuria.^[9] The latex exuded from this plant has been used as an abortifacient and as a purgative, and also used in treatment of ulcers,

leprosy, paralysis, and rheumatism. The leaves and latex of this plant are used as fish poison by the people of Malaysia, India, and New Caledonia. In Thailand, the wood and bark is used as a cure for flatulence.^[7] In Sri Lanka, the root pounded with ginger has been used to treat swellings of hands and feet, and the smoke obtained from the burning wood is used to cure leprosy.^[18] A milky sap or latex exuded from the plant can cause temporary blindness if it comes in contact with the eye and can also cause skin blisters and irritation, thus also showing the poisonous nature of the plant.^[19] The latex being poisonous in nature is used as a fish poison as well as a dart poison. According to the Indian “materia medica,” a soft reddish substance (“Tejbala”) which is obtained from the lower part of the trunk of *E. agallocha* was used as a reputed “aphrodisiac tonic.”^[5] The

Table 1: Taxonomical classification of *Excoecaria agallocha* L.

Kingdom	Plantae
Phylum	Charophyta
Class	Equisetopsida
Subclass	Magnoliidae
Order	Malpighiales
Family	Euphorbiaceae
Genus	<i>Excoecaria</i>
Species	<i>Excoecaria agallocha</i>

Table 2: Vernacular names of *Excoecaria agallocha* L.

Sanskrit	Agaru, gangwa, gaourai
Hindi	Gangiva, tejbala
Bengali	Gewa
English	Milky mangrove, blind-your-eye mangrove, river poison tree
Malayalam	Komatti, Kammetti, Kannampotti

Table 3: Geographical distribution of *Excoecaria agallocha* L.

Zone	Zonal distribution
Asia-temperate	China - Guangdong, Guangxi, Hainan; Japan - Ryukyu Islands; Taiwan
Asia-tropical	Indian Subcontinent: India - Andhra Pradesh, Goa, Karnataka, Kerala, Maharashtra, Orissa, Pondicherry, Tamil Nadu, West Bengal, Andaman and Nicobar; Sri Lanka; Bangladesh South Eastern Asia: Cambodia; Myanmar; Thailand; Vietnam; Indonesia; Malaysia; Papua New Guinea; Philippines
Australia	Australia - New South Wales, Northern Territory, Queensland, Western Australia
Pacific	South-Western Pacific: Fiji; New Caledonia; Niue; Tonga

Table 4: Botanical features of *Excoecaria agallocha* L.

Plant part	Morphological description
Branches	Lenticellate, glabrous
Stem	Bark exudate rapid and copious, sometimes deciduous
Roots	Lateral roots spreading and intermingled with each other, supraterranean bands produce elbow-shaped pegs instead of pneumatophores
Leaves	Leaves alternate, ovate-elliptic or orbicular, apex shortly acuminate, base narrowed, margin entire or sinuate-crenate, 3-8 cm×1.5-3 cm, glabrous, petiolate
Flowers	Flowers unisexual: Male flowers in catkin spikes, fragrant, yellow, 2-3 mm across, stamens 3, filaments free Female flowers in axillary raceme, pale green, 2.5-3.5 mm across, pedicellate, calyx 3-lobed, ovary 3-celled, trifold style
Fruits and seeds	Fruits 3-lobed, about 8 mm diam. Seeds about 4 mm long. Radicle about 1 mm long



Figure 1: Branch of *Excoecaria agallocha* L. showing leaves and twigs (Sundarban, October 2015)

people of Burma use the leaves to treat epilepsy. In Solomon Islands, the latex exuded from the plant is mixed with coconut milk which is used as a powerful emetic and purgative. The Malays treat itching and skin infection by the oil distilled from the woods. The roots of the plant are used to treat toothache and swellings^[20] as well as used as an ingredient of embrocations.^[21]

Phytochemistry

The chemical constituents of *E. agallocha* L., include mainly diterpenoids, terpenoids, flavonoids, alkaloids, tannins, and some other compounds.^[8,22-55] The details of their names are given in Table 5. The chemical structures of some isolated compounds are given in Figure 2.

Table 5: Phyto-constituents isolated from *Excoecaria agallocha*

Chemical compounds isolated	References
Diterpenoids	
3-oxo- <i>ent</i> -13 β -epi-8 (13)-epoxy-15-chloro-14-hydroxylabdan-3-one	[22]
<i>ent</i> -15-chloro-13,14-dihydroxylabdan-8 (9)- β -en-3-one	[22]
<i>ent</i> -15-chloro-labd-8 (9) β -ene-3 α ,13,14-triol	[22]
8,13-epoxy-3-nor-2,3-seco-14-epilabden-2,4-olide	[22]
<i>ent</i> -3-oxo-13- β -epi-manoyl oxide (ribenone)	[8,22,24,28]
<i>ent</i> -3 β -hydroxy-13- β -epi-manoyl oxide (ribenol)	[22,28]
(13R,14S)- <i>ent</i> -8 α ,13;14,15-diepoxy-13- β -epi-labda-3-one (excoecarin B)	[22,29,32]
<i>ent</i> -16-hydroxy-3-oxo-13- β -epi-manoyl oxide	[22,28]
<i>ent</i> -15-hydroxylabda-8 (17),13E-dien-3-one	[22,28]
labda-8 (17),13E-diene-3 β ,15-diol	[22]
<i>ent</i> -13- β -epi-8,13-epoxy-4,6 α -dihydroxy-3,4-secolabd-14-en-3-one (Agallochin M)	[23]
Methyl <i>ent</i> -13- β -epi-8,13-epoxy-2,3-secolabd-14-en-2,11-olide-3-one (Agallochin N)	[23]
<i>ent</i> -labda-8 (17),13E-diene-3 β ,15-diol	[24]
Excoecarin S	[25]
Excoecarin T1	[25]
Excoecarin T2	[25]
Excoecarin R1	[26]
Excoecarin R2	[26]
<i>ent</i> -8,13-epoxy-4-hydroxy-3,4-seco-13- β -epi-labd-14-en-3,11-olide (agallochaexcoerin A)	[8]
<i>ent</i> -8,13-epoxy-3 β -hydroxy-13- β -epi-labd-14-en-2-one (agallochaexcoerin B)	[8]
<i>ent</i> -8,13-epoxy-3 β ,11 α -dihydroxy-13- β -epi-labd-14-en-2-one (agallochaexcoerin C)	[8]
<i>ent</i> -8,13-epoxy-11 α -hydroxy-3-oxo-13- β -epi-labd-14-ene	[8]
Excoecarin F	[27]
Excoecarin G1	[27]
Excoecarin G2	[27]
<i>ent</i> -11 α -hydroxy-3-oxo-13- β -epi-manoyl oxide	[8,28]
<i>ent</i> -13- β -epi-manoyl oxide	[28]
(13R,14R)- <i>ent</i> -8 α ,13;14,15-diepoxy-13- β -epi-labda-3-one (excoecarin A)	[29]
(13R,14R)- <i>ent</i> -8 α ,13;14,15-diepoxy-13- β -epi-labda-3 β -ol (excoecarin C)	[29]
Excoecarin H	[30]
<i>ent</i> -13- β -epi-8,13-epoxy-2-hydroxylabda-1,14-diene-3-one	[31]
<i>ent</i> -13- β -epi-8,13-epoxy-14S,15-dihydroxylabdane-3-one	[31]
<i>ent</i> -13- β -epi-8,13-epoxy-2,3-secolabd-14-ene-2,3-dioic acid	[31]
<i>ent</i> -13- β -epi-8,13-epoxy-2,3-secolabd-14-ene-2,3-dioic acid 3-methyl ester	[31]
<i>ent</i> -13- β -epi-8,13-epoxy-2-oxa-3-oxolabd-14-ene-1R-carboxylic acid	[31]
8,13-epoxy-14-labden-3-one	[32]
Excolide A	[33]
11- β -epi-excolide A	[33]
11,13-di- β -epi-excolide A	[33]
Excolide B	[33]
<i>ent</i> -15,18-dihydroxylabda-8 (17),13E-diene	[34]
<i>ent</i> -11 β -hydroxy-8 (14),15-isopimaradiene-3-one	[22]
11 α ,14 α -dihydroxy-7,15-isopimaradiene-3-one (Agallochin J)	[35]
3 α ,11 α ,14 α -trihydroxyisopimara-7,15-diene (Agallochin K)	[35]
6 α ,14 α ,17-trihydroxy-7,15-isopimaradiene-3-one (Agallochin L)	[35]
3 α ,11 β -dihydroxy- <i>ent</i> -isopimara-8 (14),15-dien-2-one	[24]
Agallochaol D	[36]
Agallochaol E	[36]
Agallochaol F	[36]
Agallochaol A	[37]
Agallochaol B	[37]
Agallochaone A	[32]
Agallochaexcoerin D	[38]
Agallochaexcoerin E	[38]
Agallochaexcoerin F	[38]
Methyl <i>ent</i> -17-hydroxy-3,4-seco-14-ene-15,15-dien-3-one (Agallochin O)	[23]
<i>ent</i> -3 β ,20-epoxy-3 α ,6 α -dihydroxykaur-16-ene (Agallochin F)	[39]

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Table 5: Contd...

Chemical compounds isolated	References
<i>ent</i> -kauran-16 β -ol-3-one	[39]
Excoecarin M	[40]
Agallochaol K	[41]
Agallochaol L	[41]
Agallochaol M	[41]
Agallochaol N	[41]
Agallochaol O	[41]
Agallochaol P	[41]
<i>ent</i> -2,3-secokaur-16-en-2,3-dioic acid (excoecarin V2)	[34]
<i>ent</i> -3 β -hydroxykaur-16-en-2-one (excoecarin K)	[42]
3 β ,20-epoxy-3 α -hydroxybeyer-15-ene (Agallochin G)	[39]
3 β ,20:15R,16S-diepoxy-3 α -beyeranol (Agallochin H)	[25,39]
3 β ,20-epoxy-3 α ,6 α -dihydroxy-18-nor-beyer-15-ene (Agallochin I)	[36,39]
2-acetoxy-1,15-beyeradiene-3,12-dione	[39]
2-hydroxy-1,15-beyeradiene-3,12-dione	[39]
<i>ent</i> -3 β -hydroxybeyer-15-ene-2,12-dione	[24]
<i>ent</i> -12-oxo-2,3-secobeyer-15-ene-2,3-dioic acid	[25]
<i>ent</i> -15-epoxy-beyerane-3 α -ol	[25]
2 α ,3 α ,18-trihydroxy-3 β ,20-epoxybeyer-15-ene (excoecarin V1)	[34,36]
3 α ,18-dihydroxy-3 β ,20-epoxybeyer-15-ene (excoecarin D)	[36,42]
(15R,16S)- <i>ent</i> -15,16-epoxybeyeran-3-one (excoecarin E)	[42]
<i>ent</i> -2,3-secobeyer-15-ene-2,3-dioic acid	[34]
Stachenol	[42]
Stachenone	[42]
<i>ent</i> -3 β -hydroxybeyer-15-en-2-one	[42]
16 β -hydroxy- <i>ent</i> -atisan-3-one	[24]
Excoecarin N	[40]
<i>ent</i> -16 α -hydroxy-atisane-3,4-lactone	[43]
<i>ent</i> -16 α -hydroxy-atisane-3-one	[43]
<i>ent</i> -atisane-3 β ,16 α -diol	[43]
<i>ent</i> -3,4-seco-16 α -hydroxyatis-4 (19)-en-3-oic acid	[43]
Agallochaol Q	[41]
<i>ent</i> -3,4-seco-16 α -hydroxyatis-4 (19)-en-3-oic acid (excoecarin V3)	[34,36]
Agallochaol C	[36]
16 α -hydroxy-3,4-seco- <i>ent</i> -atis-4 (19)-en-3-oic acid (Agallochaol G)	[44]
16 α ,17-dihydroxy-3,4-seco- <i>ent</i> -atis-4 (19)-en-3-oic acid (Agallochaol H)	[44]
17-hydroxy-3,4-seco- <i>ent</i> -atis-4 (19)-en-3-oic acid (Agallochaol I)	[44]
17-hydroxy-3,4-seco- <i>ent</i> -atis-15-en-3-oic acid (Agallochaol J)	[44]
<i>ent</i> -atisane-16 α -ol	[34]
Excoecaria factor A ₁	[45,55]
Excoecaria factor A ₂	[45,55]
Excoecaria factor A ₃	[45,55]
Excoecaria factor A ₄	[45]
Excoecaria factor A ₅	[45]
Excoecaria factor A ₆	[45]
Excoecaria factor A ₇	[45]
12-deoxyphorbol 13-(3E,5E-decadienoate)	[46]
Excoecaria factor A ₈	[45]
Excoecaria factor A ₉	[45]
Excoagallochaol A	[47,50]
Excoagallochaol B	[47]
Excoagallochaol C	[47]
Excoagallochaol D	[47]
Triterpenoids	
3 β -[(2E,4E)-5-oxo-decadienoyloxy]-olean-12-ene	[48,49]
β -amyirin acetate	[48,49]
Taraxerone	[48,49]
3-epitaraxerol	[48]
Taraxerol	[48,49]
3-epilupeol	[48]
Acetylaleuritolic acid	[49]
cycloart-22-ene-3 β ,25-diol	[49]
<i>epi</i> - β -amyirin	[50]
<i>epi</i> - α -amyirin	[50]
Epitaraxerol	[50]
Epilupeol	[50]
Lupenone	[50]

Contd...

Table 5: Contd...

Chemical compounds isolated	References
Betulin	[50]
Betulone	[50]
Betulinic acid	[50]
Betulonic acid	[50]
Flavonoids	
2',4',6',4-tetramethoxychalcone	[51]
3,5,7,3',5'-pentahydroxy-2R,3R-flavanonol 3-O- α -L-rhamnopyranoside	[34]
Alkaloid	
2,4-dimethoxy-3- ψ , ψ -dimethylallyl-trans-cinnamoylpiperidide	[51]
Sterols	
β -sitostenone	[49]
(24R)-24-ethylcholesta-4,22-dien-3-one	[49]
β -sitosterol	[49]
Tannin	
3,4,5-trimethoxyphenol 1-O- β -D-(6-galloyl)-glucopyranoside	[34]
Miscellaneous	
Octacosyl (E)-ferulate	[8]
Quebrachitol	[52]
Ellagic acid	[53]
Methyl 3,4,5-trihydroxybenzoate	[34]
Excoecariphenols A	[54]
Excoecariphenols B	[54]
Excoecariphenols C	[54]
Excoecariphenols D	[54]
(9Z,12Z,15Z) 2,3dihydroxypropyl octadecatrienoate	[50]
(9Z,12Z) 2,3dihydroxypropyl octadecadienoate	[50]

Diterpenoids

Diterpenes are the most abundantly isolated secondary metabolite from *E. agallocha*.

Labdane-type diterpenes are the dominant class of diterpenes isolated. About 41 labdane-type diterpenes 1–41 were isolated from *E. agallocha*.^[8,22-34] Two new bis seco-labdane diterpenes 17 and 18 were isolated from resinous woods.^[26] Several seco-labdane diterpenes were also isolated from the same plant. New class of secolabdanoid compounds 37–40 with an unprecedented skeleton were isolated from the stems.^[33]

Fourteen isopimarane-type diterpenes 42–55 were isolated from *E. agallocha*.^[22,24,32,35-38] Roots yielded four isopimarane diterpenes 42–45,^[22,35] five isopimarane diterpenes 47–51 were isolated from stems and leaves,^[36,37] compounds 46 and 53–55 were isolated from woods,^[24,38] and compound 52 was isolated from the whole plant.^[32] Two isopimarane diterpenes 53 and 54 contains a seven membered lactone moieties.^[38]

So far, 12 kaurane-type diterpenes 56–67 were isolated from different parts of *E. agallocha*. Most of the kaurane diterpenes are ent-kaurane derivatives.^[23,34,39-42] Fifteen Beyerane-type diterpenes 68–82 were also isolated from different parts of the plant.^[24,25,34,36,39,42]

Fourteen artisane-type diterpenes 83–96 were isolated from different parts of *E. agallocha*,^[24,34,36,40,41,43,44] out of which compounds 83 and 84 are isolated from woods,^[24,40] compounds 85–88 were isolated from bark,^[43] compound 89 was isolated from the twigs and stems,^[41] and compound 96 was isolated from stems only^[34] and stems and leaves yielded five artisane diterpene 90–95.^[34,36,44]

Seven daphnane-type diterpenes 97–103 as cryptic and free skin irritant were isolated from the latex. These diterpenes are named as Excoecaria factor (A_1 – A_7) out of which Excoecaria factor (A_1 – A_3) are known.^[45,55]

A novel phorbol ester 104 was isolated from stems and leaves as the anti-HIV principle.^[46] In 1994, Karalai *et al.* isolated two new tigilane-type diterpenes 105 and 106 from the latex of *E. agallocha*.^[45]

Four diterpenoids excoagallochaols A–D 107–110 with an unprecedented skeleton were also isolated from stems and leaves of the plant.^[47,50]

Triterpenoids

Seventeen triterpenoids 111–127 were isolated from various parts of *E. agallocha*. The terpenoids isolated are oleanane, taraxerone, cycloartane, and lupane derivatives.^[48-50]

Flavonoids

Two flavonoids 2',4',6',4-tetramethoxychalcone 128^[51] and 3,5,7,3,5-pentahydroxy-2R,3R-flavanonol 3-O- α -L-rhamnopyranoside 129^[34] were isolated from this mangrove species.

Alkaloids

A piperidine alkaloid 2,4-dimethoxy-3- ψ , ψ -dimethylallyl-trans-cinnamoylpiperidide 130 was isolated from *E. agallocha*.^[51]

Sterols

Three steroidal components such as β -sitostenone 131, (24R)-24-ethylcholesta-4,22-dien-3-one 132, and β -sitosterol 133 were isolated from the stems and twigs.^[49]

Tannins

In 2003, Konishi *et al.* isolated a known tannin 3,4,5-trimethoxyphenol 1-O- β -D-(6-galloyl)-glucopyranoside 134 from the fresh stem of the plant.^[34]

Miscellaneous

Ten other compounds 135–144 were isolated from the woods. They were mainly organic acids, organic acid esters and alcohol derivatives.^[8,34,50,52-54]

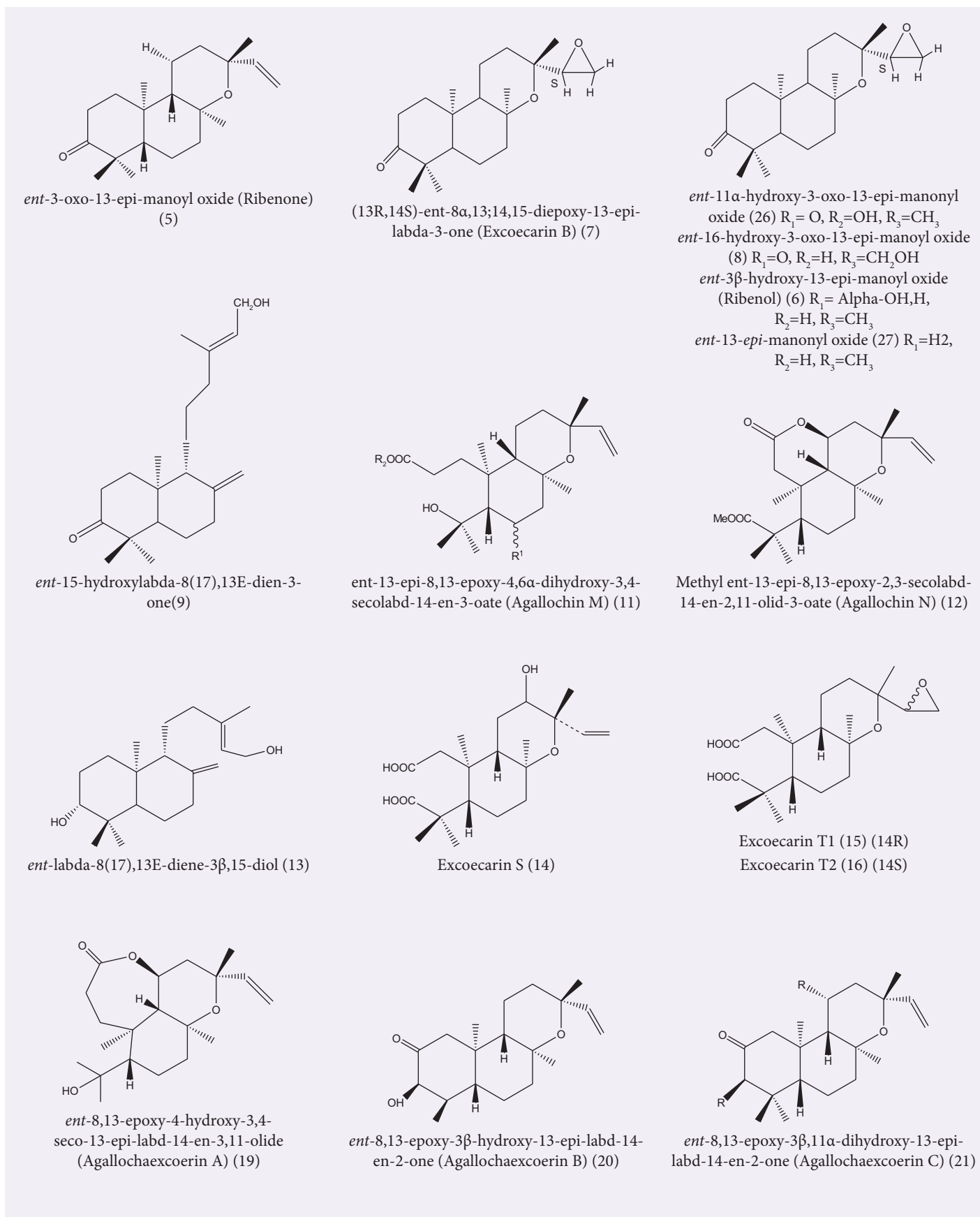


Figure 2: Chemical structures of phyto-constituents isolated from *Excoecaria agallocha* L.

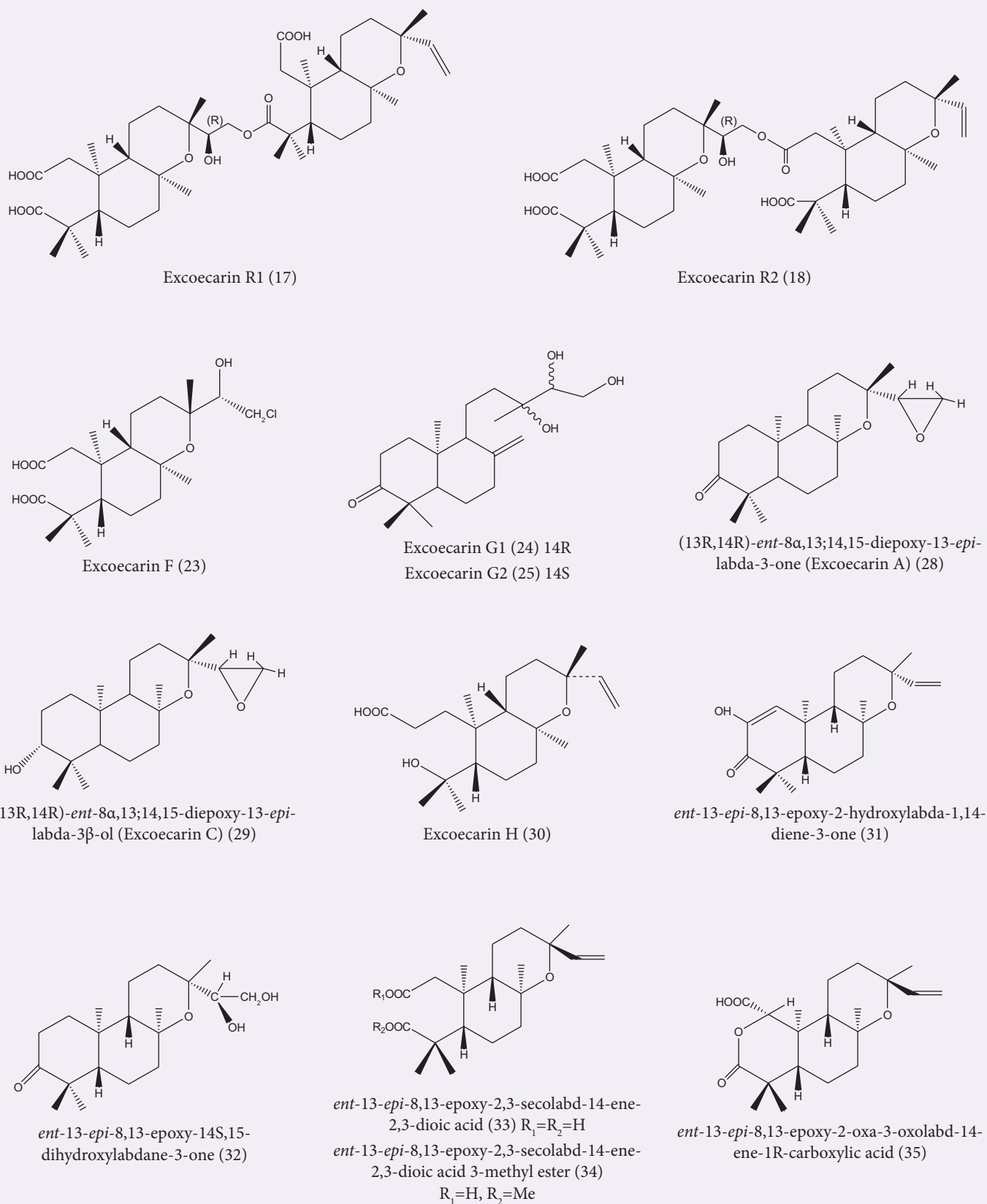


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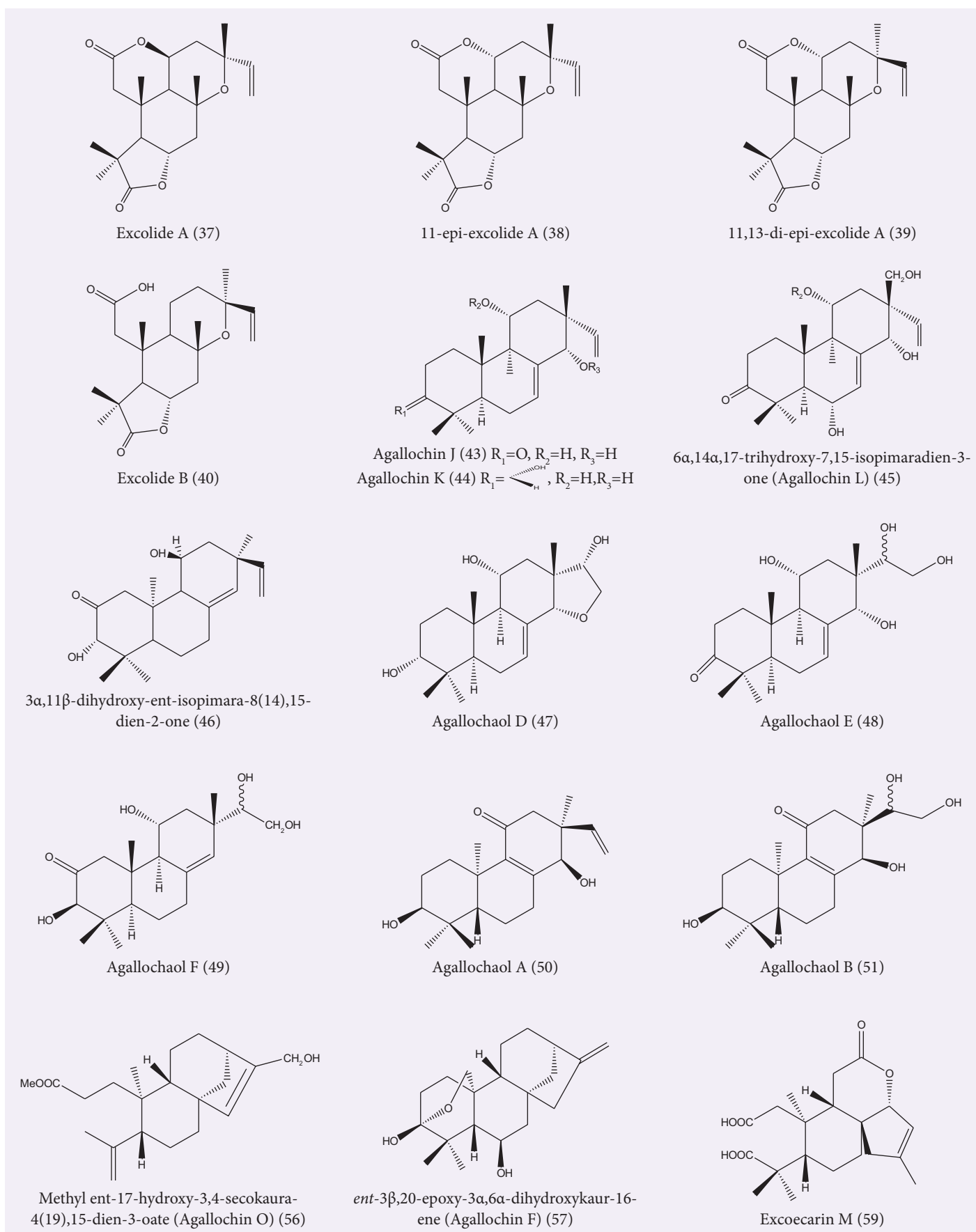


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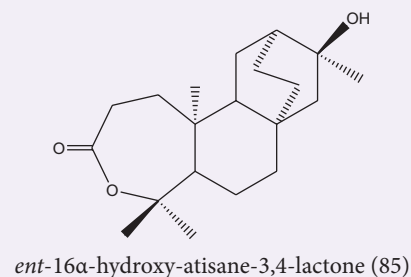
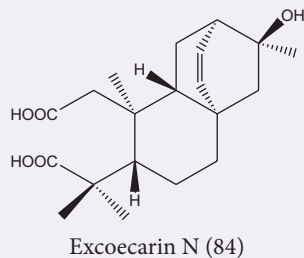
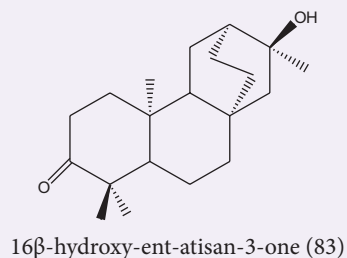
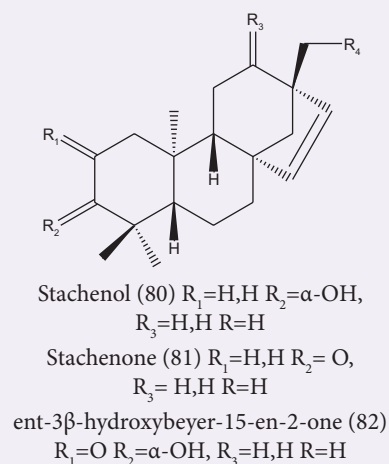
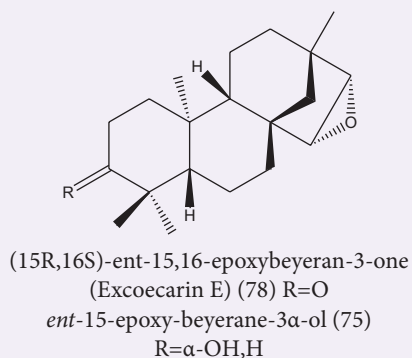
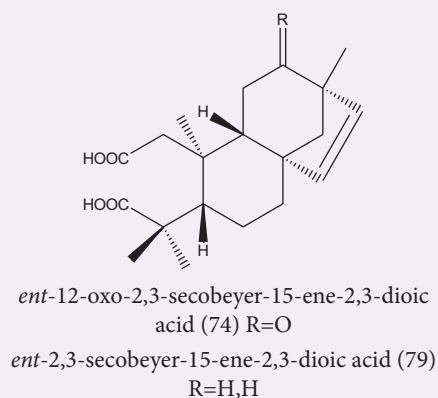
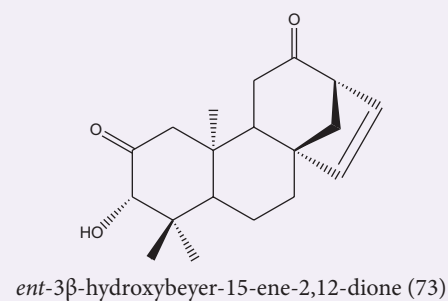
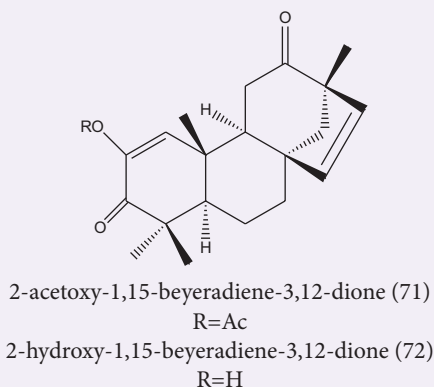
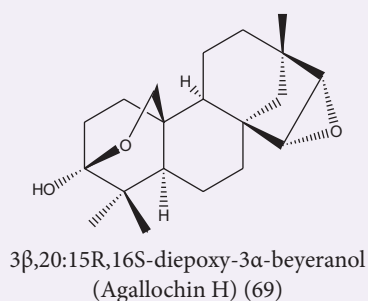
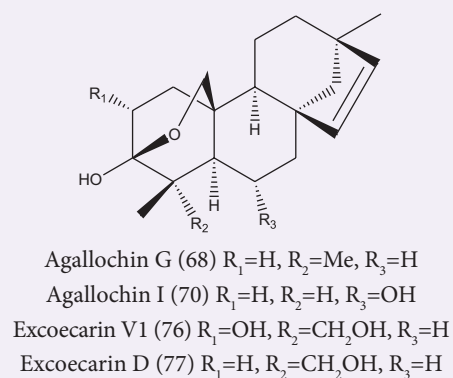
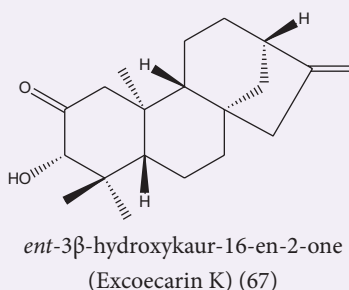
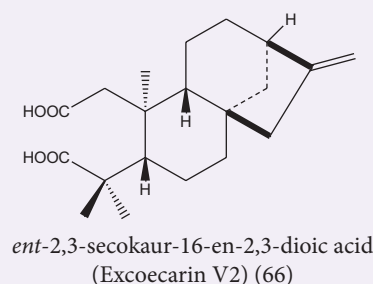
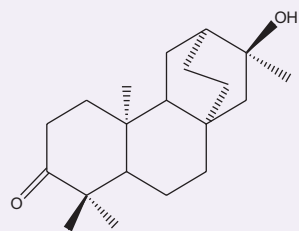
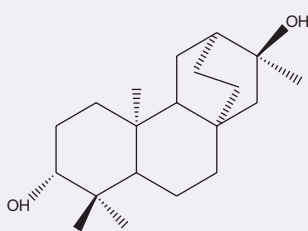


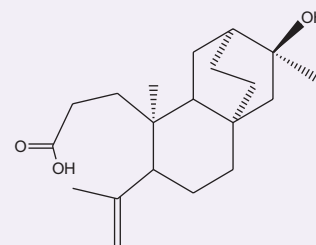
Figure 2: Contd...



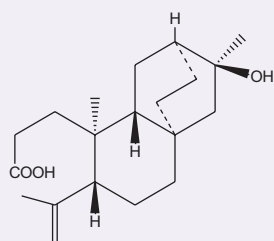
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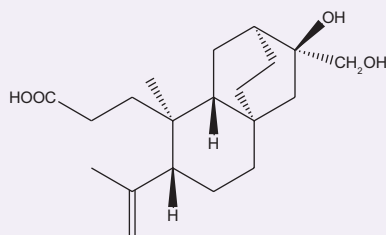
ent-atisane-3 β ,16 α -diol (87)



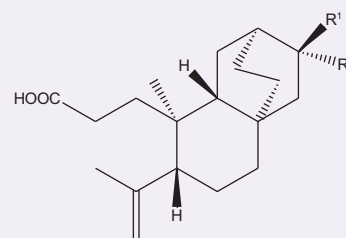
ent-3,4-seco-16 α -hydroxyatis-4(19)-en-3-oic acid (88)



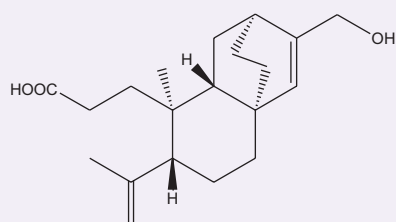
ent-3,4-seco-16 α -hydroxyatis-4(19)-en-3-oic acid (Excoecarin V3) (90)



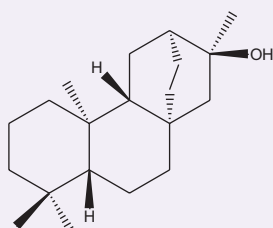
Agallochaol C (91)



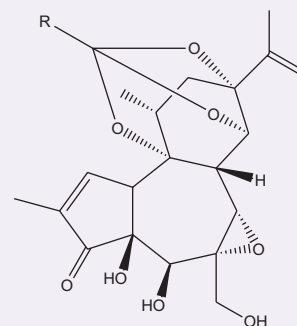
Agallochaol G (92) R₁=Me, R₂=OH
Agallochaol H (93) R₁=CH₂OH, R₂=OH
Agallochaol I (94) R₁=CH₂OH, R₂=H



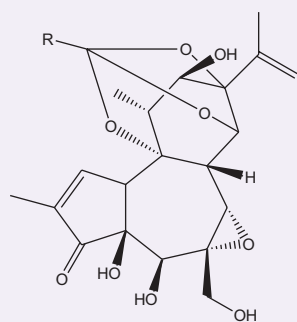
17-hydroxy-3,4-seco-*ent*-atis-15-en-3-oic acid (Agallochaol J) (95)



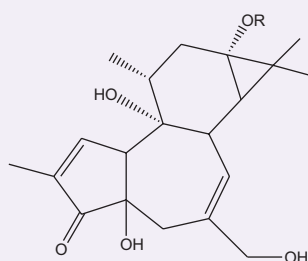
ent-atisane-16 α -ol (96)



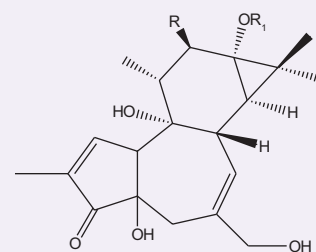
Excoecaria factor A₁ (97)
R= Me — (CH₂)₈ — (CH=CH)₃ Excoecaria factor A₂ (98)
R= Me — (CH₂)₆ — (CH=CH)₄ Excoecaria factor A₃ (99)
R= Me — (CH₂)₄ — (CH=CH)₂ Excoecaria factor A₄ (100)
R=CHO (CH=CH)₂ Excoecaria factor A₅ (101)
R=CHO — (CH=CH)₃



Excoecaria factor A₆ (102)
R=Me — (CH₂)₈ — (CH=CH)₃
Excoecaria factor A₇ (103)
R=Me — (CH₂)₆ — (CH=CH)₄



Excoecaria factor A₈ (105)
R= Me — (CH₂)₇ (CH=CH)₂ — CH₂ — CO
Excoecaria factor A₉ (106)
R=Me — (CH₂)₇ — (CH=CH)₃ CH₂ — CO



12-deoxyphorbol 13-(3E,5E-decadienoate) (104)
R=H, R₁= — C(=O) — CH₂ — (CH=CH)₂ — CH₂ — CH₂ — CH₃

Figure 2: Contd...

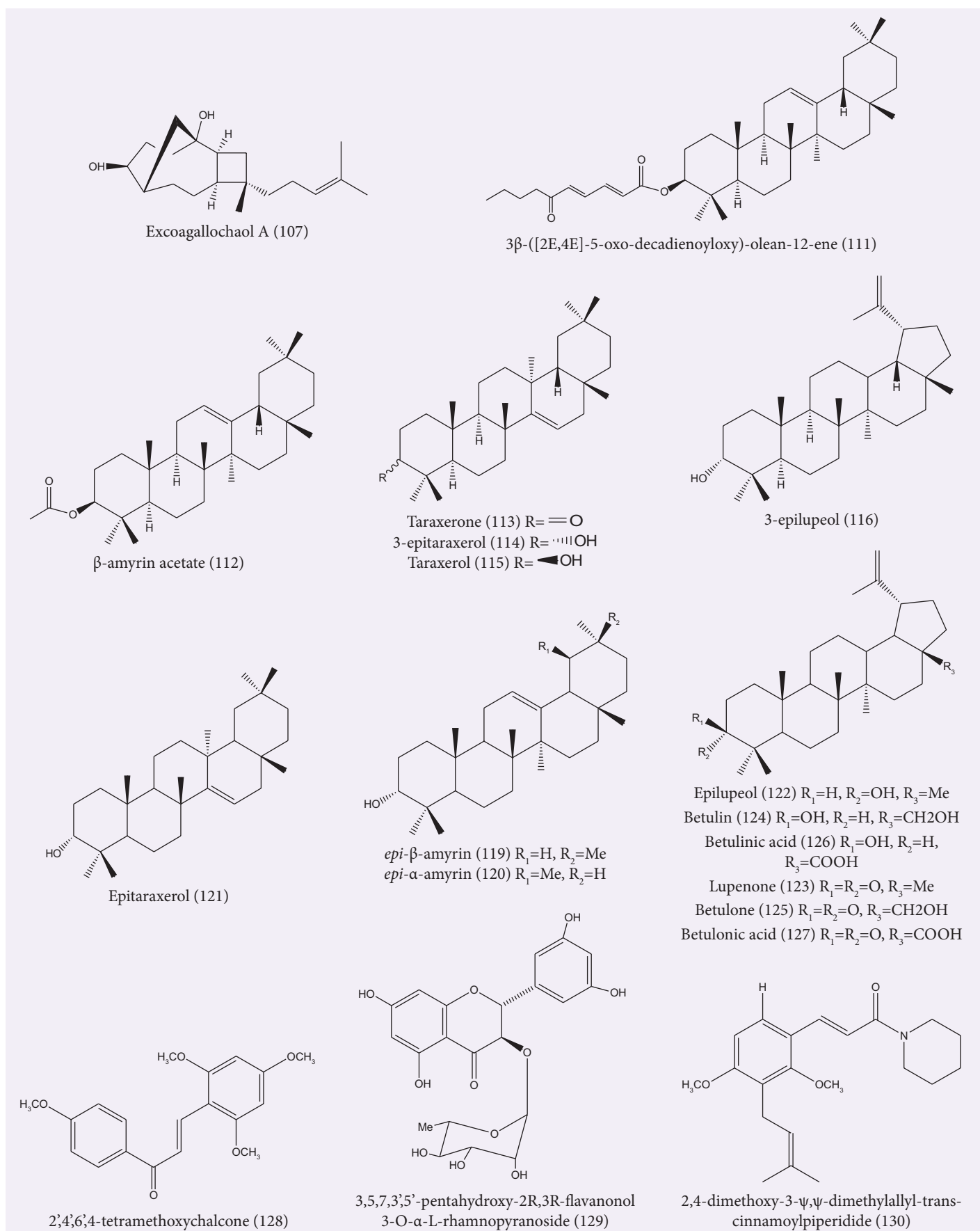


Figure 2: Contd...

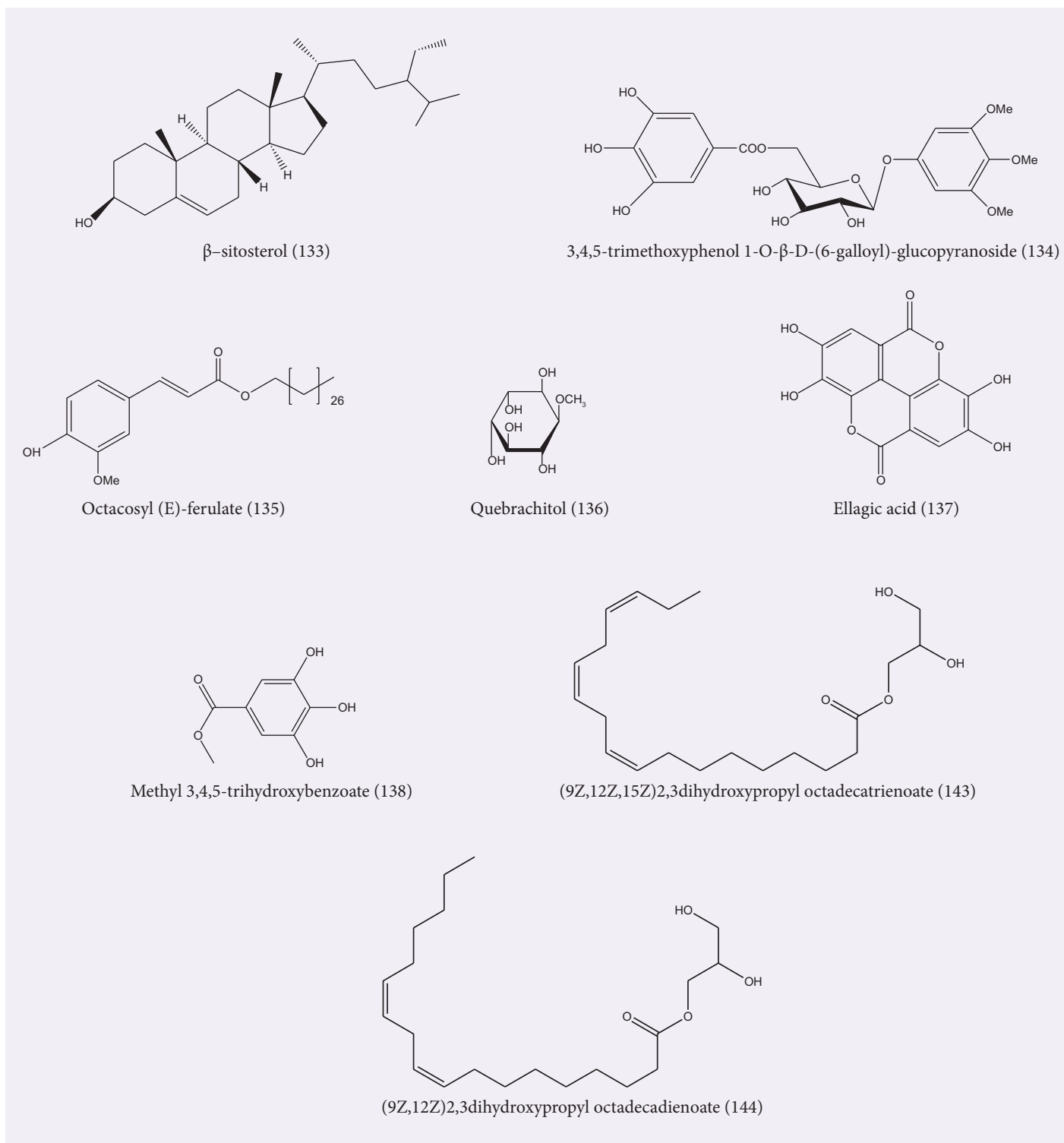


Figure 2: Contd...

PHARMACOLOGICAL ACTIVITIES

Antioxidant activity

Hossain *et al.* performed the antioxidant activity of dried powder of *E. agallocha* bark using various antioxidant models such as reducing power, 1,1-diphenyl-2-picryl-hydrazil (DPPH) free radical scavenging activity, and measurement of total antioxidant activity. The result

showed that distilled water and ethanol fractions had high antioxidative activities compared to other fractions such as hexane, chloroform, and ethyl acetate.^[56] Antioxidant activities using DPPH radical scavenging assay were performed by Rajaram Panneerselvam *et al.* on field and micropropagated plant leaves of *E. agallocha*. The result revealed that DPPH radical scavenging effect was greater in micropropagated plants (IC₅₀ value of 10.2, 10.8, and 17.4) than in the field grown plants.

Ascorbic acid content was more in micropropagated plants 18 mg/plant when compared to field grown plants. Highest total phenolic content was also recorded in micropropagated plant (207 and 205 mg/GAE/g) than in field grown plant.^[17] Antioxidant activities were further determined on the aqueous extract which revealed that the antioxidant activity using DPPH radical scavenging activity, reducing power, and hydrogen peroxide scavenging activity increases in a dose-dependent manner. The phenol content was also determined which was 2.215 ± 0.049 , 1.625 ± 0.006 , 1.405 ± 0.006 , and 1.109 ± 0.049 for acetone, ethanol, methanol, and aqueous extract, respectively.^[57] Poorna *et al.* performed the antioxidant activity on the leaves, and the result revealed that the methanol extract has a strong DPPH free radical scavenging activity (IC_{50} value 67.50 μ g/ μ l). The methanolic extract also showed potent nitric oxide radical inhibition (IC_{50} value 4.8 μ g/ μ l), lipid peroxidation inhibition (IC_{50} value 100 μ g/ μ l), and metal chelating effect (IC_{50} value 2.47 μ g) in a dose-dependent manner.^[7] In 2012, Patra *et al.* reported the antioxidant activity of thin layer chromatography fraction of *E. agallocha*, leaves which showed that 23.36% DPPH radical scavenging activity at 40 μ l concentration.^[58]

Antimicrobial activity

Antimicrobial activity was evaluated by Varaprasad Bobbarala *et al.* on hexane, chloroform, and methanol extracts of *E. agallocha* leaves. Twelve microorganisms were taken to study antibacterial and antifungal activity, i.e. for antifungal – *Acremonium strictum*, *Aspergillus flavus*, *Aspergillus niger*, *Candida albicans*, *Curvularia lunata*, *Fusarium oxysporum*, *Macrophomina phaseolina*, *Penicillium expansum*, *Rhizoctonia solani*, *Ustilago maydis*, and *Xanthomonas campestris* and for antibacterial – *Lactobacillus fermentum* and *Staphylococcus aureus*. The result revealed that methanol extract exhibited higher activity compared to hexane and chloroform extract.^[59] Antimicrobial activities of the mangrove plant were further evaluated against selected fish pathogens such as *Chryseobacterium indologenes*, *Flavobacterium indicum*, *Chryseobacterium gleum*, and *Elizabethkingia meningoseptica* previously named *Flavobacterium meningosepticum*. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration of the methanolic extract were 3.12 mg/ml and 6.25 mg/ml, respectively. Zone of inhibition was significantly different ($P < 0.05$) according to the doses (100, 300, and 500 mg/ml) of the crude extracts. The highest activity (LC_{50}) recorded was 94.19 mg/ml. Thus, *E. agallocha* methanolic leaves extract showed high antimicrobial activity against these fish pathogens.^[60] Eighty percent methanolic extract of wild grown plants, leaf derived callus, and *in vitro* raised plant leaves of *E. agallocha* were prepared and evaluated for antibacterial activity against *Bacillus cereus*, *Bacillus subtilis*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *S. aureus*, *Salmonella typhi*. The result revealed that methanolic extract of leaf derived callus showed more antibacterial activity than the wild grown and *in vitro* raised plants.^[17] Antimicrobial properties of *E. agallocha* fatty acid methyl esters (FAMES) extracts were studied by Agoramoorthy *et al.*, and the results showed that FAME extracts exhibited strong antimicrobial activities against 11 selected microorganisms of which seven were bacteria such as *B. subtilis*, *Bacillus pumilus*, *S. aureus*, *Micrococcus luteus*, *K. pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli* and four were yeast such as *C. albicans*, *Candida tropicalis*, *Candida krusei*, and *Candida parapsilosis*. The mean zone of inhibition of the extract calculated ranged between 7.3 and 16.6 mm.^[18] Ethanol extracts of fresh and dried leaves, roots, and stems were screened for antibacterial activity against *Vibrio cholerae*, *S. aureus*, *S. typhi*, *Proteus* sp., and *Enterobacter* sp. The result showed that in the dried plant sample, the leaf part showed more antibacterial activity against all the test organisms compared to the fresh plant extracts.^[61] Chloroform leaves extract were screened for

antibacterial activity against various fish pathogens such as *B. subtilis*, *Aeromonas hydrophila*, *Vibrio parahaemolyticus*, *Vibrio harveyi*, and *Serratia* sp. The result showed that the third fraction exhibited the maximum activity which was 12 mm against *V. parahaemolyticus*, followed by *V. harveyi* (10 mm), *B. subtilis* (10 mm), and *A. hydrophila* (8 mm).^[62] The antibacterial activity of the aqueous leaf extracts was assayed *in vitro* by disc diffusion method against five bacterial strains. The Gram-negative bacterial strains revealed the zone of inhibition, i.e. *E. coli* (17 mm), *P. aeruginosa* (15 mm), *K. pneumoniae* (16 mm), and Gram-positive bacterial strains showed *S. aureus* (15 mm), *B. subtilis* (14 mm) at 128 μ g concentration. The MIC of Gram-negative and Gram-positive organisms were analyzed by microtiter plate technique. The MIC values for *E. coli* was <2 μ g, *B. subtilis* was 128 μ g, *S. aureus* was 256 μ g, *P. aeruginosa* was 128 μ g, and *K. pneumoniae* was 32 μ g.^[63] *E. agallocha* leaves extracts also showed significant antifungal activity against four fungal pathogens *R. solani*, *Fusarium udum*, *M. phaseolina*, *Sclerotium rosi*, whereas there was no activity shown in fungal pathogen *Alternaria alternata*.^[64] Ethanol:methanol (5.6:1) extract of leaves, stem, and root was screened for antifungal activity by the spore formation inhibition in *Alternaria tenuis*, *Helminthosporium oryzae*, *F. oxysporum*, and inhibition of budding in yeast (*Saccharomyces cerevisiae*). The result showed significant antifungal activity in a dose dependent manner.^[65] In 2012, Patra *et al.* reported the antimicrobial activity of the leaves against various bacterial pathogens such as *S. aureus* and *B. subtilis*, *Shigella flexneri*, *P. aeruginosa*, and *E. coli*. The result showed positive for *S. aureus* and *P. aeruginosa*.^[58]

Anti-inflammatory activity

Babuselvam *et al.* studied the acute inflammatory properties of ethanol in water (3:1) extract of different parts such as latex, leaves, and seed of *E. agallocha* which showed statistically significant activity at a dose of 500 mg/kg in carrageenan induced rat paw edema model at 4 h as compared to the control causing an inhibition of 63.15%, 62.15%, and 69.69% in latex, leaves, and seeds, respectively. Whereas in cotton pellet-induced granuloma test, the seed extract showed maximum activity at the dose of 500 mg/kg which was 57.03% compared to control.^[66]

Analgesic activity

The analgesic effect of ethanol:water (3:1) extract of leaves, seeds, and latex of *E. agallocha* was studied by Babuselvam *et al.*, out of which the seed extract significantly decreased the number of writhes in 20 min and also increased the percentage of inhibition in acetic acid writhing test in test animals. Moreover, in the tail immersion model, the seed extract at the concentration of 500 mg/kg possesses maximum activity (80.29%) as compared to control.^[66] Crude alcoholic bark extract at 300 mg/kg dose showed maximum time needed for the response against thermal stimuli 6.72 ± 0.43 s compared to diclofenac sodium 8.20 ± 0.21 s in the hot plate test. In acetic acid-induced Writhings test in mice, 500 mg/kg dose of the bark extract showed maximum reduction (53.87%). In the tail immersion method, 300 mg/kg dose of the alcoholic bark extract showed the highest activity.^[67]

Antiulcer activity

Antiulcer activity of *E. agallocha* leaves was studied in nonsteroidal anti-inflammatory drug induced ulcer in rats where the result showed that the leaves extract increases the mucosal defense in the gastric area as well as able to lower the acidity. Thus, the leaves of the plant can be used as an antiulcerogenic agent.^[68] The alcoholic extract of the bark showed significant antiulcer activity against acetylsalicylic acid induced ulceration.^[67]

Anticancer activity

In 2011, Patil *et al.* reported anticancer activity using MTS *in vitro* assay on activity-guided fraction of ethanol extract of *E. agallocha* stem, and the result revealed strong activity against pancreatic cancer cell lines Capan-1 and Miapaca-2 with IC₅₀ values of 4 µg/ml and 7 µg/ml, respectively.^[69] In 2012, anticancer activity on human lung cancer cell lines of the ethanol stem extract were reported by Patil *et al.* where the result showed potent cytotoxic activities in a dose-dependent manner and also caused p21-mediated G1 arrest in p53^{-/-} cells and apoptotic programmed cell death in p53^{+/+} cells.^[16]

Anticancer activity was also tested on leaf extract by Batsa and Periyasamy in cell line model, and the result revealed high activity at lower concentration when compared to higher concentration. At a particular higher concentration, the cell viability was more in methanol extract than the chloroform extract.^[70]

Antireverse transcriptase activity

Antireverse transcriptase activity of the ethanol extract of *E. agallocha* stems was reported by Patil *et al.* in 2011. The result showed that activity guided ethanol fraction of stem ethanol extract has a potent antireverse transcriptase activity.^[69] A novel phorbol ester was isolated which was a potent *in vitro* inhibitor of HIV-1 replication as measured by the inhibition of supernatant reverse transcriptase and p24 levels (IC₅₀ 6 nm).^[46]

Antihistamine-release activity

Antihistamine-release activity of *E. agallocha* bark on ionophore A23187-induced histamine-release assay model was studied by Hossain *et al.*, and the result revealed that distilled water and ethanol showed high antihistamine-release activity compared to other fractions such as hexane, chloroform, and ethyl acetate.^[56]

Antifilarial activity

E. agallocha methanolic leaves extract showed significant antifilarial activity in a dose dependent response which was evident by death caused in the stages of development of *Setaria digitata*, which is a metazoan filarial parasite. After 24 h of treatment with the methanolic leaves extracts at a concentration of 10, 50, and 100 µg/ml about 30%, 75%, and 90% of the developmental stages of *S. digitata* were found dead, respectively.^[57]

DNA damage protective activity

DNA damage protective activity of *E. agallocha* leaves was reported by Poorna *et al.* in 2012, where significant activity were shown by the water fraction of the leaves extract which was successful in protecting DNA damage.^[7]

Antidiabetic activity

Antidiabetic activity of leaves of *E. agallocha* was studied by Thirumurugan *et al.* in alloxan-induced diabetic mice, and the result revealed that the ethanolic leaves extract at the dose of 500 mg/kg has significant hypoglycemic activity in both the normal and alloxan-induced diabetic mice.^[71]

Antitumor protecting activity

Seven diterpenoids were isolated from *E. agallocha* resinous woods which showed significant inhibitory effects on Epstein-Barr virus (EBV) activation which were induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) a tumor promoter. Furthermore, ent-3 β-hydroxy-15-beyerene-2-one (82) exhibited remarkable antitumor promoting activity *in vivo* in a two-stage

carcinogenesis test of mouse tumor using 7,12-dimethylbenz[a]anthracene (DMBA) as an initiator and TPA as a promoter.^[72]

Several diterpenoids were isolated from mangrove plant *E. agallocha* and their inhibitory effects on the induction of EBV early antigen (EBVEA) in Raji cells were also examined. Of these diterpenes, the seco-labdane-type diterpenoid, Excoecarin T1 (15) exhibited a potent inhibitory effect on EBVEA induction and a significant antitumor-promoting effect in the two-stage carcinogenesis test in mouse using DMBA as an initiator and TPA as a promoter.^[73]

CONCLUSION

Different parts of *E. agallocha* L., including the leaves, roots, woods, stems, bark, latex, and seeds have been reported to have therapeutic potential in traditional medicine for the treatment of various diseases. These include antioxidant, antimicrobial, anti-inflammatory, analgesic, antiulcer, anticancer, antireverse transcriptase, antihistamine-release, antifilarial, DNA damage protective, antidiabetic, and antitumor protecting activities. Several bioactive compounds belonging to various chemical groups were isolated from different parts of the plant. Mostly diterpenoids were isolated and they were mainly labdane, isopimarane, kaurane, beyerane, artisane, daphnane, tigilane type diterpenoids. Other phytoconstituents isolated are mainly triterpenoids, flavonoids, alkaloids, sterols, tannins, and few other miscellaneous compounds (Organic acids, organic acid esters, and alcohol derivatives). This review highlights several pharmacological and phytochemical studies that have demonstrated the therapeutic potential and phytochemical constituents of *E. agallocha* L.

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Conflicts of interest

There are no conflicts of interest.

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